UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/775,169	02/11/2004	Michael E. Burczynski	AM101080	1858

25291 7590 06/23/2008

WYETH
PATENT LAW GROUP
5 GIRALDA FARMS
MADISON, NJ 07940

EXAMINER	
HIBBERT, CATHERINE S	

ART UNIT	PAPER NUMBER
1636	

MAIL DATE	DELIVERY MODE
06/23/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/775,169	BURCZYNSKI ET AL.	
	Examiner	Art Unit	
	Catherine S. Hibbert	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 January 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,6,7,9,10,17-24,26 and 27* is/are pending in the application.

4a) Of the above claim(s) *6 and 18-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 7, 9-10, 17, 21-24 and 26-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 29 January 2008 has been entered.

Applicants' Amendments to the Claims filed 29 January 2008 have been received and entered. Claims 2-5, 8, 11-16 and 25 are cancelled. Claims 1, 6-7, 9-10, 17-24 and 26-27 are pending. Claims 6 and 18-20 are withdrawn. Claims 1, 7, 9-10, 17, 21-24 and 26-27 are under examination in this Office Action.

Response to Arguments

The objection to the oath/declaration has been withdrawn based on Applicants submittal of a corrected oath filed 29 January 2008.

The Double Patenting rejection in the previous action has been withdrawn based on the cancellation of the cited conflicting Claims 1-3 in co-pending Application 10/793,032 and therefore Applicant's request for an abeyance, filed 29 January 2008, regarding the Double Patenting rejection is moot. However, please note that a new Double Patenting rejection directed to the presently amended instant claims and present co-pending claims of co-pending Application 10/793,032 is presented herein below.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 7, 9-10, 17, 21-24 and 26-27 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement for reasons of record and for reasons below. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The rejection of cancelled claims 4, 11, 13 and 25 is moot.

Applicants' arguments have been fully considered but are respectfully not found persuasive.

Applicants response is to traverse the 112, first paragraph, (enablement) rejection. Regarding the breadth of claims, Applicants "assert that the claims as amended are not overly broad in view of the disclosure and the ordinary knowledge in the art". Applicants submit that the base claim 1 "is currently directed to a method of detecting *in vivo* CCI-779 activity in a patient having renal cell carcinoma (RCC), including the steps of generating an expression profile of any one or more of Table 5 markers in a peripheral blood sample of the RCC patient and comparing that profile to a baseline reference profile from one or more patients prior to receiving CCI-779 treatment, such that a significant difference between the reference profile and expression profile indicates *in vivo* CCI-779 activity". As such, Applicants argue that

"the claim is hence directed to those patients suffering from RCC, which is described for example at paragraphs [0036] - [0039] and exemplified at Example 2 (paragraph [0464])" and continue that "the reference expression profile is limited to a base-line expression profile determined from samples obtained from RCC patients prior to CCI-779 treatment, which is exemplified, for example, at Example 3, paragraph [0469]". Furthermore, Applicants state that "the markers to which the claim are directed are those markers which are significantly differentially expressed in PBMCs from RCC patients treated with CCI-779" and continue that "those markers are explicitly defined in Tables 2-5, and their structures are clearly depicted in the sequence listing as SEQ ID NOs: 1-310". In addition, Applicants argue that "while Table 5 does depict a list of more than one marker, such a list is fully enabled by the instant specification" and furthermore, that "the skilled artisan would readily recognize that the change in gene expression of any one or more of those markers upon administering CCI-779 to a RCC patient, relative to the base-line reference, indicates an *in vivo* effect of CCI-779".

Regarding guidance and working examples, Applicants "note that the claims as amended provide a reference expression profile that is established from PBMCs taken from patients prior to CCI-779 administration, which is exemplified, for example, in working Example 3".

Furthermore, Applicants traverse "the assertion by the Office that the claims require a nexus between *in vivo* CCI-779 activity as a change in marker expression in PBMCs, and an effect of CCI-779 on RCC, whereby a change in PBMC markers mirrors an effect on RCC tumors". Applicants further argue that "the claims as presented do not

provide that such a nexus be made", because "the claims merely recite an *in vivo* effect on PBMC marker gene expression".

Regarding the "State of the Prior Art and Level of Predictability in the Art", Applicants "traverse the Office's assertion that the *in vivo* effects of CCI-779, as provided in the claims, must include experimental correlation between an observed effect in marker expression in PBMCs (which is supported in the instant specification with working examples) and an effect in a tumor/RCC". Applicants contend that "the present claims do not require per se that PBMCs act as surrogates in the determination of efficacy of CCI-779 treatment in patients with RCC", and that therefore Applicants "submit that the requirement that the specification must enable the determination of the effectiveness of CCI-779 therapy toward RCC or any other solid tumor is not proper in view of the pending claims".

Regarding the amount of Experimentation Needed to practice Applicants invention, Applicants "submit that the pending claims provide for assessing an expression profile in PBMCs after CCI-779 treatment, compared to a base-line reference expression profile obtained prior to CCI-779 treatment". Applicants continue that "the gene expression markers, which were empirically determined to change in response to CCI-779 administered to patients, are presented, for example, in Tables 2-5", and continue that "each of the markers were empirically determined to change significantly in response to CCI-779 treatment, thereby actually showing an *in vivo* effect due to CCI-779". Thus, Applicants again traverse the assertion "that a nexus be established between the *in vivo* effects as expressed in PBMCs and an effect upon the

solid tumor", and conclude that "the effect of CCI-779 upon the PBMCs, *in vivo*, either directly or indirectly, in terms of differential marker expression, has been established in the working examples and in the resultant tables 2-5".

Applicants' arguments have been fully considered but are not persuasive because enablement is considered in view of the Wands factors (MPEP 2164.01(A)) . These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art, the amount of experimentation necessary and the relative skill levels of those in the art. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

The instant Claims 1, 7 and 9, 22-23, are drawn to a method for detecting *in vivo* CCI-779 activity in a patient having renal cell carcinoma (RCC), the method comprising: (a) generating an expression profile (determined by RT-PCR or immunoassay) of at least one CCI-779 activity gene selected from Table 5 in a peripheral blood (whole blood) sample obtained from the patient having RCC and at a stage of treatment (8/16 weeks after initiation) with CCI-779; (b) comparing the expression profile of the at least one CCI-779 activity gene generated in step (a) to a reference expression profile of said at least one CCI- 779 activity gene; and (c) detecting in vivo CCI-779 activity in the patient based on the comparison result from step (b), wherein: (i) a statistically significant change in the expression profile of said at least one CCI-779 activity gene compared to the reference expression profile is indicative of the *in vivo* CCI-779 activity, and (ii) the reference expression profile is a baseline-expression profile of said at least

one CCI-779 activity gene in a peripheral blood sample isolated from one or more patients before CCI-779 treatment. Claim 10 further limits the method according to claim 1 to wherein the reference expression profile is a baseline- expression profile of said at least one CCI-779 activity gene in a peripheral blood sample isolated from said patient before CCI-779 treatment. Claim 21 further limits the method of claim 1 to wherein the at least one CCI-779 activity gene comprises profilin 1.

The instant Claims 17 and 26/27 are drawn to a method for identifying genes modulated by CCI-779, the method comprising: (a) obtaining a peripheral blood sample from a patient having renal cell carcinoma (RCC) and at a stage of treatment (8/16 weeks after initiation) with CCI-779; (b) generating an expression profile of the peripheral blood sample obtained in step (a) and; (c) comparing said expression profile generated in step (b) to a reference expression profile of a reference peripheral blood sample from said patient to identify one or more differentially expressed genes, wherein the reference peripheral blood sample is isolated from one or more patients before CCI-779 treatment. Claim 24 further limits the method of claim 17 to wherein the reference expression profile is a baseline expression profile of a peripheral blood sample obtained from said patient before CCI-779 treatment.

Nature of the Invention and Breadth of the Claims: The claims are drawn to methods comprising a comparison between an expression profile from at least one "CCI-779 activity gene" (selected from among the 310 genes listed in Table 5) in a peripheral blood sample of a patient having a solid tumor and "at a stage of treatment with CCI-779" to a "reference expression profile". While claim 21 is drawn to such a

method comprising the use of profilin-I, the rest of the claims encompass the use of any gene or set of genes from selected from among the 310 genes listed in Table 5. The nature of the invention is complex in that gene expression patterns involving potentially thousands of different genes are involved. Furthermore, the PBMCs from which the expression patterns will be obtained are not themselves diseased and are only presumed to comprise genes which can be modulated by the CCI-779 in a way that is indicative of a "CCI-779 activity gene." Thus, the invention is broad in scope and very complex.

Guidance Provided by the Specification and the Existence of Working Examples: The specification teaches that the invention employs PBMCs "as surrogate tissues for the detection of *in vivo* activities of CCI-779 or other drugs" (see pages I-2, paragraph [0004]). The specification further teaches that the invention employs systematic gene expression analysis to identify genes whose expression in peripheral blood can be modulated by a therapeutic agent such as CCI-779 (see page 5, paragraph [0019]). These "drug activity genes" can further be utilized such that changes in the peripheral blood expression profile of such genes are indicative of the *in vivo* activity of the drug therapy (page 4, [0017]). The specification discloses 310 CCI-779 activity genes in Table 5, so identified (see page 39-45, Table 5, paragraph [0041]).

On the whole, the disclosure appears to assert that, because differences in gene expression can be determined among genes expressed in PBMCs from a subject with a non-blood disease pre- and post-drug therapy, and because these genes can be identified, differences in PBMC gene expression before and after drug treatment would

be indicative of the *in vivo* effect of a drug therapy upon any given non-blood disease. However, the specification does not provide a single working example of such a complex method, wherein the genes identified before and at different stages of CCI-779 treatment are indicative of the *in vivo* activity of the drug therapy utilized, especially with regard to the effect of the drug therapy upon the solid tumor. Nor does the specification teach how a difference in one gene's expression (be it profilin-1 or any other gene selected from Table 5) should or could be measured such that the difference is indicative of CCI-779's activity on the solid tumor.

State of the prior art and level of predictability in the art: The "predictability or lack thereof" in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention. If one skilled in the art can readily anticipate the effect of a change within the subject matter to which the claimed invention pertains, then there is predictability in the art. On the other hand, if one skilled in the art cannot readily anticipate the effect of a change within the subject matter to which that claimed invention pertains, then there is lack of predictability in the art. Accordingly, what is known in the art provides evidence as to the question of predictability. The physiological art is recognized as unpredictable (MPEP 2164.03). As set forth in In re Fischer, 166 USPQ 18 (CCPA 1970), compliance with 35 USC §112, first paragraph requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art. In cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other

embodiments can be made without difficulty and their performance characteristics predicted by resorting to known scientific laws. In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved.

The question of predictability in the instant case has to do with whether the skilled artisan would be able to extrapolate from the disclosed CCI-779-modulated genes and the knowledge available in the art regarding the correlated effects of drug therapy upon a renal cell carcinoma (RCC tumor) and the simultaneous changes in PBMC gene expression, such that the skilled artisan could practice the claimed method to determine if changes in the PBMC expression profiles before and and/or at different stages of drug treatment were indicative of the *in vivo* activity of the drug on RCC.

The claimed method proposes to use any "drug activity gene" selected from Table 5 (or profilin/ claim 21) as a biomarker or surrogate endpoint for efficacy in the treatment of RCC with CCI-779 drug therapy. The art recognizes that before a putative biomarker can be used as a surrogate endpoint it must be validated as such. Wagner (Dis. Markers 18(2):41-46, 2002, made of record in the Office Action mailed 4 April 2007) acknowledges in the Abstract, "Putative biomarkers are typically identified because of a relationship to known or hypothetical steps in a pathophysiologic cascade. Biomarker discovery can also be effected by expression profiling experiment using a variety of array technologies and related methods." However, Wagner cautions, "A rational basis for recommending the use of a putative biomarker does not guarantee the utility of the biomarker or its qualification as a surrogate endpoint" (paragraph bridging

the left and right columns on page 43) and "Biomarkers require validation in most circumstances" (paragraph bridging pages 43-44). Frank et al. (Nature Rev. 2:566-580, 2003, made of record in the Office Action mailed 4 April 2007) concurs, stating, "The standard concepts of test-re-test reliability and validity apply with equal force to clinical biomarkers as they do in any assay system" and, "The work required to establish the reliability and validity of a new biomarker should not be underestimated in general, and in particular needs of planning for each combination of clinical indication and mechanism of action" (paragraph bridging the left and right columns on page 568). Feng et al. (Pharmacogenomics 5:709-719, 2004, made of record in the Office Action mailed 4 April 2007) teaches, "The development and validation of clinically useful biomarkers from high-dimensional genomic and proteomic information pose great research challenges. Present bottle necks include: that few of the biomarkers showing promise in initial discovery were found to warrant subsequent validation. A molecular profiling approach, although promising, has a high chance of yielding biased results and overfitted models" (Abstract).

Viewed as a whole, the art clearly teaches that the utility of a putative biomarker as a surrogate endpoint for any disease state is unpredictable and must be validated. With regard to the use of biomarkers in renal cell carcinoma (RCC), an article published after Applicant's effective filing date describes "disease-associated" expression profiles in peripheral blood mononuclear cells (PBMCs) from patients with advanced renal cell carcinoma (Twine et al. Cancer Research 63(18) :6069-6075, 2003, made of record in the Office Action mailed 4 April 2007). However, Twine et al do not disclose that such

gene expression patterns can be used to detect RCC in a patient. Rather, Twine et al teach the presence of expressed, disease-associated genes in the PBMCs of RCC patients, which if additional experiments were to bear such findings out, could "represent the foundation on which to build disease-specific gene sets that can be used as part of a molecular diagnosis of disease using peripheral blood" (see page 6075, last paragraph, as well as page 6074, Figure 2). Twine et al. also teach that "it is currently unknown whether in the context of RCC or any other active solid tumor burden there exists correspondingly distinct markers of gene expression in the PBMCs of affected individuals" (page 6069, first column, first paragraph). Thus, even after Applicant's effective filing date the art does not recognize gene expression profiles from PBMCs which are necessarily diagnostic of renal cell carcinoma. It would therefore be an even larger hurdle to determine from among those putative biomarkers of RCC, those genes which could act as surrogates for the efficacy of a drug therapy upon RCC.

Thus, the state of the prior art with regard to the use of surrogate endpoints in general was underdeveloped and unpredictable at the time of Applicant's filing; the state of the art was silent with regard to the use of PBMC biomarkers to determine the efficacy of drug therapy on RCC in particular.

Amount of Experimentation Necessary: Given the underdeveloped state of the art and the level of unpredictability in the art, one of ordinary skill in the art would have been required to perform an undue amount of experimentation in order to first, accurately determine gene expression differences in PBMCs of patients with RCC before and/or after different stages of drug treatment. Then, once differences in gene

expression were found (if any), one of ordinary skill in the art would have to determine which of those difference were indeed indicative of the drug therapy and could therefore be used as an indication of the drug's activity *in vivo*. The *in vivo* drug activity on PBMC gene expression and upon the RCC would need to be correlated. This amount of experimentation is exacerbated by the breadth of the claims, which would require one of ordinary skill in the art to determine which genes from Table 5 (or profilin) were associated before and/or at different stages after treatment with CCI-779 for RCC.

"It must be remembered...that ' [p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. Genentech, 108 F.3d at 1366 (quoting Brenner v. Manson, 383 U.S. 519, 536 [148 USPQ 689] (1966) (stating, in context of the utility requirement, that 'a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion')). Thus, while the need for some experimentation is by no means necessarily fatal, 'reasonable detail must be provided in order to enable members of the public to understand and carry out the invention.' Id." University of Rochester v. G.D. Searle & Co., 68 USPQ2d 1424 at 1436 (W.D.N.Y. 2003).

Regarding Applicants arguments, it is particularly noted that Applicants argument that it is not required "that a nexus be established between the *in vivo* effects as expressed in PBMCs and an effect upon the solid tumor", is not persuasive because without a connection between the drug efficacy for the treatment of the RCC, one of ordinary skill in the art would clearly not be apprised of how to make and *use* Applicants

invention. The instant disclosure provides a single real-world use for the claimed method, which is to detect *in vivo* activities of CCI-779. Therefore, because the first paragraph of 35 USC 112 requires that the disclosure teach the skilled artisan how to make and use the claimed invention, the specification in the instant case must teach the skilled artisan how to practice the claimed method such that it can be *used* to detect *in vivo* activities of CCI-779 as asserted in the specification.

Given no more than what is provided in the instant application and the relevant art, the skilled artisan would not know how to practice the claimed invention (i.e., which differences in gene expression to use in combination with which solid tumors such that the difference(s) in gene expression were indicative of the drug therapy's efficacy *in vivo*. Given the unpredictable nature of the invention and the broad scope of the claims, the amount of experimentation would clearly be undue. Therefore, the disclosure fails to adequately enable the claims and the claims are properly rejected under 35 U.S.C. §112, first paragraph.

Claims 1, 7, 9-10, 17, 21-24 and 26-27 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement for reasons of record and for reasons above.

New Grounds of Objection/Rejection

Claim Objections

Claim 10 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is

required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Because the limitation of Claim 10 has been incorporated into the instant amendment of Claim 1, Claim 10 no longer further limits the subject matter of Claim 1.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 7, 10 and 17 (and Claims 24 and 26-27 insofar as they depend from Claim 17) are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 7 recites the limitation "the peripheral blood sample" in line 1. The antecedent basis for this limitation in the claim is unclear because Claim 1 refers to two distinct “peripheral blood samples”, one in step (a) and another in step (c), part (ii).

Claim 10 recites the limitation "said patient before CCI-779 treatment" in line 3. There is insufficient antecedent basis for this limitation in the claim because Claim 1 recites “one or more patients before CCI-779” and therefore it is unclear which of these one or more patients is providing the antecedent basis for “said patient” in Claim 10.

Claim 17 recites the limitation "from said patient" in step (c), line 2 and the limitation "from one or more patients" in step (c), line 4. The antecedent basis for these limitations in the claim is unclear because it is unclear how the reference peripheral

blood sample could be referring to said patient from step (a) coincidentally with "one or more patients" cited in step (c), line 4.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1 and 10 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 21 and 34 of copending Application No. 10/793,032. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the 10/793,032 application are drawn to methods comprising the comparison of an expression profile of at least one gene in a peripheral blood sample of a patient to a reference expression

profile of said at least one gene, wherein said at least one gene is differentially expressed in peripheral blood mononuclear cells (PBMCs) of a patient who has the non-blood disease and who is being treated by a drug therapy as compared to PMBCs of said patient before said drug therapy. Furthermore, both sets of claims encompass embodiments wherein the drug therapy is CCI-779 therapy and wherein the non-blood disease is a solid tumor. The co-pending Claims 21 and 34 differ from the instant application because they are directed to a solid tumor but not limited to the specific type of tumor (RCC) as presently in the amended instant claims. However, the limitation of the RCC type of solid tumor was previously cited in the co-pending claims (e.g. cancelled Claim 3) and therefore it renders the instant claims obvious over the co-pending claims in light of the co-pending disclosure. Therefore, these claims anticipate claims 1 and 10 of the instant application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Catherine S. Hibbert, Ph.D., whose telephone number is (571)270-3053. The examiner can normally be reached on M-F 8AM-5PM, EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, Ph.D., can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-

273-8300.Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Respectfully submitted,

Catherine S. Hibbert/AU1636

/Daniel M Sullivan/
Primary Examiner, Art Unit 1636